A Consistent Approach for the Application of Pharmacokinetic Modeling in Cancer and Noncancer Risk Assessment

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Physiologically based pharmacokinetic modeling provides important capabilities for improving the reliability of the extrapolations across dose, species, and exposure route that are generally required in chemical risk assessment regardless of the toxic end point being considered. Recently, there has been an increasing focus on harmonization of the cancer and noncancer risk assessment approaches used by regulatory agencies. Although the specific details of applying pharmacokinetic modeling within these two paradigms may differ, it is possible to identify important elements common to both. These elements expand on a four-part framework for describing the development of toxicity: *a*) exposure, *b*) tissue dosimetry/pharmacokinetics, *c*) toxicity process/pharmacodynamics, and *d*) response. The middle two components constitute the mode of action. In particular, the approach described in this paper provides a common template for incorporating pharmacokinetic modeling to estimate tissue dosimetry into chemical risk assessment, whether for cancer or noncancer end points. Chemical risk assessments typically depend upon comparisons across species that often simplify to ratios reflecting the differences. In this paper we describe the uses of this ratio concept and discuss the advantages of a pharmacokinetic-based approach as compared to the use of default dosimetry. ***Key words*: dose–response assessment, interspecies extrapolation, pharmacokinetics, physiologically based pharmacokinetic modeling, risk assessment, tissue dosimetry. *Environ Health Perspect* 110:85–93 (2002). [Online 18 December 2001]**
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The process of assessing the health risks associated with human exposure to toxic environmental chemicals inevitably relies on a number of assumptions, estimates, and rationalizations. Some of the greatest challenges result from the necessity to extrapolate from the conditions in the studies providing evidence of the toxicity of the chemical to the anticipated conditions of exposure in the environment or workplace. For risk assessments based on animal data, the most obvious extrapolation that must be performed is from the tested animal species to humans; however, others are also generally required: from high dose to low dose, from one exposure route to another, and from one exposure time frame to another. Physiologically based pharmacokinetic (PBPK) modeling provides a powerful method for increasing the reliability of these extrapolations (*1–3*). The inherent capabilities of PBPK modeling are particularly advantageous for cross-species extrapolation: the physiological and biochemical parameters in the model can be changed from those for the test species to those that are appropriate for humans to provide a biologically meaningful animal-to-human extrapolation. However, it is important to recognize that a full PBPK model may not always be necessary to support a pharmacokinetic risk assessment. In some cases only a simple compartmental pharmacokinetic description is needed; an excellent example has been published for the case of cadmium (*4–5*).

Simple pharmacokinetic approaches have occasionally been used by regulatory agencies in cancer risk assessment; for example, the use of metabolized dose for trichloroethylene (*6,7*). The first case in which an agency has used a full PBPK approach was in the U.S. Environmental Protection Agency's (U.S. EPA) latest revision of its inhalation risk assessment for methylene chloride (*8*). The decision to use the PBPK approach in this case was made only after a period of considerable controversy, including a workshop sponsored by the National Academy of Sciences at which the usefulness of PBPK modeling for chemical risk assessment was discussed. The scientific consensus following the workshop was that "relevant PBPK data can be used to reduce uncertainty in extrapolation and risk assessment"(*9*). In 1989, after a detailed multiagency evaluation of the available PBPK information and a review by the U.S. EPA Scientific Advisory Board, the U.S. EPA revised the inhalation unit risk and risk-specific air concentrations for methylene chloride in its Integrated Risk Information System (IRIS) database, citing the PBPK model developed by Andersen et al. (*10*). The resulting risk estimates were lower than those obtained by the default approach by nearly a factor of 10. This difference was driven by the lower rate of metabolism in humans compared to mice, giving rise to the reactive intermediate associated with the tumors. Subsequently, an adaptation of the same PBPK model was used by the Occupational Safety and Health Administration (OSHA) in making rules for methylene chloride (*11*). More recently, the U.S. EPA has used PBPK models for vinyl chloride (*12*) and 2-butoxyethanol (*13*) in its risk assessments for these chemicals.

The advantages of applying PBPK modeling in risk assessment have been discussed both for cancer (*9,14–17*) and noncancer end points (*18–21*). In addition, the use of PBPK modeling has been recommended to improve route-to-route extrapolation (*22*) and the estimation of risk for chemical mixtures (*23*). Recently, there has been an increasing focus on harmonization of the cancer and noncancer risk assessment paradigms used by regulatory agencies in the United States.

The specific details of applying PBPK modeling within these two paradigms may differ. For example, lifetime average daily dose is used for cancer risk assessment, whereas average daily dose during exposure is used for noncancer. Nevertheless, it is possible to identify important elements common to both (*24*). The starting point for a harmonized approach is a four-part framework for organizing qualitative and quantitative analyses of data available for chemical risk assessment. The four elements are exposure, tissue dosimetry, toxicity process, and response (Figure 1). Tissue dosimetry information is obtained from quantitative pharmacokinetic analyses. Quantitative descriptions of the processes leading to toxicity are referred to as pharmacodynamic analyses. These two elements link the exposure with the response and are often described as the mode of action of a chemical (although it should be noted that mode of action has also been used synonymously with toxicity process). The four elements form the basis for analyzing toxicity

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information in animals or humans and for carrying out extrapolations between the species. They represent the minimum elements necessary for risk assessment purposes; elaborated series of steps can also be given that more completely describe the biological processes. In the following discussion, we describe the key elements of the approach for applying pharmacokinetic modeling of tissue dosimetry to dose–response assessment in a format equally applicable to both cancer and noncancer end points.

Dose Metric Selection

The ultimate aim of using pharmacokinetic modeling in risk assessment is to provide a measure of dose that better represents the "biologically effective dose"; that is, the dose that causally relates to the toxic outcome. The improved dose metric can then be used in place of traditional dose metrics (such as concentration or exposure dose) in an appropriate dose–response model to provide a more accurate extrapolation to the human exposure conditions of concern. Implicit in any application of pharmacokinetics to risk assessment is the assumption that the toxic effects can be related to the concentration of an active form of the substance in the mechanistically relevant tissue. Often the tissue in which the chemical is active is the same tissue in which the toxic effects occur; this is the target tissue. Sometimes, the target for the effects of a chemical and the organ in which the toxicity are observed are different (e.g., effects on brain may alter hormonal signaling observed as toxicity in a reproductive organ). In this case, the term "target tissue" must be used with care because the concept is altered from its traditional usage. Similar responses are expected to be produced at equivalent tissue exposures regardless of species, exposure route, or experimental regimen unless there are pharmacodynamic differences between animal species (*3,25,26*). The motivation for applying pharmacokinetics in risk assessment is the expectation that the observed effects of a chemical will be more simply and directly related to a measure of target tissue exposure than to a measure of administered dose (*1,27*).

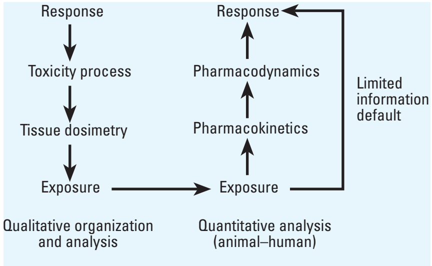
Response
Toxicity process
Tissue dosimetry
Exposure
Response
Pharmacodynamics
Pharmacokinetics
Exposure
Limited information default
Qualitative organization and analysis
Quantitative analysis (animal–human)

Figure 1. Framework for using mode of action information in dose–response analysis.

The specific nature of the relationship between target tissue exposure and response depends on the chemical mechanism of toxicity, or mode of action, involved. Many short-term, rapidly reversible toxic effects, such as acute skin irritation or acute neurologic effects, may result primarily from the current concentration of the chemical in the tissue. In such cases, the likelihood of toxicity from a particular exposure scenario can be conservatively estimated by the maximum concentration (C_{MAX}) achieved in the target tissue (*28–30*). In contrast, the acute toxicity of highly reactive chemicals, as well as many longer-term toxic effects such as tissue necrosis and cancer, may be cumulative in nature, depending on both the concentration and duration of the exposure. A simple metric for such cases is the area under the concentration curve (AUC) in the tissue, which is defined mathematically as the integral of the concentration over time (*27,31,32*). This mathematical form implicitly assumes that the effect of the chemical on the tissue is linear over both concentration and time. The use of the AUC represents an extension of the concept, developed from observations of the effects of chemical warfare gases (*33*), that toxicity is proportional to the product of the concentration and time of exposure ($C \times T$). For developmental effects, the chemical time course may also have to be viewed in the context of the window of susceptibility for a particular gestational event (*34*).

An important factor in selecting an appropriate dose metric is to determine the toxicologically active form of the chemical. In some cases, a chemical may produce a toxic effect directly, either through its reaction with tissue constituents (e.g., ethylene oxide) or its binding to cellular control elements (e.g., dioxin). Often, however, it is metabolism of the chemical that leads to its toxicity. In this case, toxicity may result primarily from reactive intermediates produced during the process of metabolism (e.g., chlorovinyl epoxide produced from the metabolism of vinyl chloride) or from the toxic effects of stable metabolites (e.g., trichloroacetic acid produced from the metabolism of trichloroethylene). The selection of the dose metric, that is, the active chemical form for which tissue exposure should be determined and the nature of the measure to be used (e.g., C_{MAX} or AUC) is the most important step in applying pharmacokinetics in risk assessment.

Dose metrics must be selected to be consistent with the modes of action for the chemical being evaluated. No single dose metric will always be appropriate for a given effect, although consistency is expected for chemicals acting via the same mechanism. The U.S. EPA (*35*), in a joint effort with scientists from several other agencies, prepared a review paper on cross-species extrapolation in cancer risk assessment which concluded that

> … [T]issues experiencing equal average concentrations of the carcinogenic moiety over a full lifetime should be presumed to have equal lifetime cancer risk.

The use of the term "carcinogenic moiety" in this statement reflects the concern that the dose metric should be representative of the active form of the chemical. For example, the use of the lifetime average daily concentration for the parent chemical would be appropriate for a directly genotoxic chemical such as ethylene oxide, which is detoxified by metabolism; however, it would not be appropriate for a chemical such as vinyl chloride, which requires metabolic activation to be genotoxic. In the latter case, increasing metabolism would increase the exposure to the genotoxic species but would decrease a dose metric based on the concentration of the parent chemical. In such a case, where a reactive species produced during the metabolism of a chemical is responsible for its carcinogenicity, an appropriate cancer dose metric would be the lifetime average daily production of metabolite in the target tissue divided by the volume of the tissue, as described in the pharmacokinetic risk assessment for methylene chloride (*10*). Similar considerations apply in the case of noncancer risk assessment, except that the dose metrics are only averaged over the duration of the exposure (acute, subchronic, or chronic) or the critical developmental window, not over a full lifetime (*28*).

Finally, it should be noted that although C_{MAX} and AUC are the most commonly applied metrics for tissue exposure, other dose metrics might sometimes be more appropriate, particularly for chemicals with a mode of action related to some aspect of their interaction with a receptor. In such cases, time above a critical concentration (TACC) or average receptor occupancy might be more appropriate (*36,37*). Unfortunately, the more we attempt to include pharmacodynamic processes into a dose metric (e.g., receptor occupancy), the more difficult it usually becomes to collect the data necessary for its use in each of the relevant species. Of the many possible dose metrics, typically only C_{MAX}, AUC, and TACC can be estimated from the kinds of data currently available on chemicals. Although we have discussed these dose metrics in terms of the target tissue, there is often a simple proportional relationship between the blood level and the tissue level so the dose metrics used are in blood rather than in tissue. Typically, data on blood concentrations are more often available, particularly in humans, making it possible to validate model predictions.

The Ratio Concept in Risk Assessment

Although it is crucial that the dose metric properly represents the essential nature of the biologically effective dose, as described above, it is often possible to simplify the actual dose metric calculation by recognizing that quantitative risk assessment is fundamentally based on a ratio, specifically, the ratio of the dose metric value for the exposure of concern to the value for the exposure (or exposures) defining the toxicity. Typically, the exposures defining the toxicity might be the no-observed-adverse-effect level (NOAEL) in an animal experiment or the doses in a cancer bioassay, whereas the exposure of concern might be a lifetime continuous human exposure. Any factors that do not change across the conditions of these exposures will not effect the ratio of the dose metrics, and thus will not impact the risk assessment.

For example, the ultimate dose metric for a particular toxicity might be based on the concentration of the chemical in the target tissue. However, an acceptable dose metric might be based on the chemical's blood concentration as long as the relationship between the blood concentration and target tissue concentration could be expected to be the same in both the animal toxicity study and in human exposure. In fact, this is probably a reasonable assumption across different exposure conditions in a given species: namely, that the concentrations would be related by the tissue:blood partition coefficient. However, although tissue:air partition coefficients for volatile lipophilic chemicals appear to be similar in dogs, monkeys, and humans (*38*), human blood:air partition coefficients appear to be roughly one-half of those in rodents (*39*). Therefore, the human tissue:blood partition would probably be about twice that in the rodent. Thus, if the model was used for extrapolation from rodents to humans, this 2-fold difference could be factored into the analysis as an adjustment to the blood concentration dose metric.

The dose metric for a reactive metabolite provides another example of the use of this ratio concept: the amount of metabolism divided by the volume of the tissue is used as a surrogate for the average concentration of the reactive species, on the assumption that other factors remain constant. That is, we assume that the stoichiometric yield of the reactive species and its reaction rate are invariant across species and over the exposure conditions being modeled.

Use of the ratio concept can greatly simplify risk assessment applications of pharmacokinetic modeling for developmental toxicity or teratogenicity studies. Although it may seem necessary to use a model that includes compartments for the developing fetus, this may not always be the case. For some chemicals, the maternal blood or plasma concentration profile can provide an adequate surrogate for the fetal exposure (*40,41*). An important point is that symmetric diffusion limitation, such as might be expected for placental transport of many environmental contaminants, does not affect the AUC in the tissue. That is, while diffusion-limited transport across the placenta might delay the achievement of the maximum concentration in the fetus as compared to the maternal blood, the AUC in the fetus would bear the same relationship to the AUC in the blood as it would in the case of flow-limited transport. Moreover, for exposures of sufficient duration to reach steady state, the steady-state fetal concentration will be completely determined by partitioning and will not be affected by diffusion-limited transport. For many chemicals, the only important pharmacokinetic complication associated with fetal development is the resulting increase in the total volume of distribution for the chemical. This complication may be ignored for risk assessment purposes because the effect can be similar in both the toxicity study and the human exposure of concern.

Impact of Pharmacokinetics in Risk Assessment

Pharmacokinetics has been addressed differently in the default noncancer and cancer approaches. The standard paradigm for noncancer risk assessment rarely considers chemical-specific pharmacokinetic information; typically, a NOAEL or lowest-observed-adverse-effect level (LOAEL) derived from data for the exposure route of interest is simply adjusted by the application of generic uncertainty factors (UFs) to obtain reference concentrations (RfCs) or reference doses (RfDs). Individual UFs of from 1 to 10 are applied for various potential sources of uncertainty including use of a LOAEL, extrapolation to a longer exposure duration, extrapolation from animals to humans, human variability, and database limitations. Typically the total UF (the product of the individual UFs) is restricted to a maximum of 3,000 (*42*).

In this paradigm, little attention has been given to incorporating knowledge of the mode of action or the dosimetry of the active chemical form in target tissues in these calculations. The selection of UFs has also generally failed to consider chemical-specific mechanistic information or pharmacokinetic data. One exception is the focus in the revised RfC process on delivered dose adjustments for inhaled materials (*42*).

In the traditional paradigm for cancer risk assessment in the United States, dose–response modeling was used to calculate a carcinogenic potency based on tumors observed in animal bioassays or human epidemiology studies. In the case of animal studies, "body surface area" scaling (multiplying by the cube root of the ratio of the animal and human body weights) was used to obtain a human equivalent dose (HED) (Table 1, Appendix 1). Dose–response modeling was then performed on the HEDs using the linearized multistage model (*43*). For inhalation studies, conversion from inhaled concentration to absorbed dose was performed by a rudimentary calculation involving the ventilation rate, body weight, and fraction absorbed. As mentioned above, chemical-specific pharmacokinetic information has occasionally been used in this process; for example, the calculation of metabolized dose in the risk assessment for trichloroethylene (*6,7*), and the use of a PBPK model in the risk assessment for methylene chloride (*8*). The guidelines for carcinogen risk assessment recently proposed

Table 1. Examples of interspecies scaling based on body weight ratios.*

Species	BW^b	ADD for species (mg/kg/day)	A/H ratio $(A/H)^{1-b}$	H/A ratio $(H/A)^{1-b}$	HED (mg/kg/day)
$b = 1$	BW^1		$(A/H)^0$	$(H/A)^0$	
Human	70	1	1	1	1
Rat	0.25	1	1	1	1
Mouse	0.030	1	1	1	1
$b = 3/4$	$BW^{3/4}$		$(A/H)^{1/4}$	$(H/A)^{1/4}$	
Human	24.20	1	1.0	1.0	1
Rat	0.354	1	0.244	4.1	0.244
Mouse	0.0721	1	0.144	7.0	0.144
$b = 2/3$	$BW^{2/3}$		$(A/H)^{1/3}$	$(H/A)^{1/3}$	
Human	16.5	1	1.0	1.0	1
Rat	0.401	1	0.153	6.5	0.153
Mouse	0.0988	1	0.075	13.3	0.075

Abbreviations: ADD, average daily dose; *b*, scaling exponent; BW, body weight; A, animal body weight; H, human body weight.

*Representative values of body weight for different species have been assumed; the ADD was assumed to be 1 mg/kg/day. The HED for each animal species' ADD was calculated using Equation 8 in Appendix 1 and the assumed values of BW and ADD shown above.

by the U.S. EPA (*44*) would appear to provide the flexibility necessary to move forward in this area. Under the new guidelines, multiple options are available for performing a carcinogenic dose–response assessment including a linear approach similar to the traditional cancer paradigm, and a margin of exposure (MOE) approach more similar to the noncancer paradigm. The selection of the dose–response approach to be used with a particular chemical is determined on the basis of the information available on the carcinogenic mode of action of the chemical, which considers both pharmacokinetic and mechanistic information.

Cross-species extrapolation. In the traditional default risk assessment approaches, all chemicals are implicitly treated as if the observed toxicity is produced directly by the parent chemical itself (*3*). This implicit assumption that the parent chemical is directly toxic is true even in the new RfC dosimetry guidelines (*42*), which differentiate respiratory effects from extra-respiratory effects and include different defaults for chemicals based on their solubility and reactivity. However, a risk assessment that considers pharmacokinetics must necessarily also consider the mode of action, at least to the extent of identifying the active form of the chemical for which the dosimetry should be performed.

To demonstrate the importance of considering pharmacokinetics and mode of action in dose–response risk assessment, we used PBPK models for methylene chloride (*10*), trichloroethylene (*21*), and vinyl chloride (*12*) to determine general expectations for the cross-species dosimetry for one class of chemicals, the volatile lipophilic solvents. All three of these chemicals are considered category 3 gases (relatively water-insoluble chemicals that achieve a steady state during inhalation exposure) in the U.S. EPA dosimetry guidelines (*42*). In a standard risk assessment, the animal-to-human dosimetry adjustment for each of these chemicals would be performed in exactly the same way. For example, for noncancer analyses, time-weighted average (TWA) exposure concentration for inhalation and milligrams per kilogram per day administered dose for oral exposure are used, regardless of the nature of the toxic end point or the mechanism of toxicity.

In contrast to the simplicity and uniformity of the default approaches, a pharmacokinetic approach requires the application of scientific judgment to select the appropriate option for each toxic effect of a chemical. Table 2 provides a comparison of the default and PBPK-based approaches as a function of the type of toxicity and the exposure route based upon the analyses for methylene chloride, vinyl chloride, and trichloroethylene.

For the purpose of this comparison, we assumed that the acute, reversible neurologic effects of these chemicals result from the direct toxicity of the parent chemical; thus, an appropriate dose metric would be either the C_{MAX} or the AUC of the parent chemical in the brain or, as discussed above, in the blood as a surrogate for the brain. For the calculations used to prepare Table 2, we selected the AUC because it is more analogous to the TWA calculation typically used for duration adjustment. In contrast, because we assumed that the production of reactive species during metabolism was responsible for the chronic liver toxicity of methylene chloride and vinyl chloride, we used the average daily amount of metabolism divided by the volume of the liver as the dose metric. Finally, we assumed that the development of liver toxicity from trichloroethylene resulted from the activity of the stable metabolite, trichloroacetic acid; therefore, we used the average daily AUC for trichloroacetate in the liver as the dose metric.

To obtain the comparisons shown in Table 2, we used the PBPK models to determine dose metrics for a typical exposure scenario in the mouse and rat. The models were then rerun for the same exposure scenario but with human parameters, and the concentration or dose was varied until the human dose metric was the same as that obtained for the mouse and rat. These two pharmacokinetically determined human equivalent concentrations (HECs) or doses (HEDs), one for the mouse and one for the rat, were then compared to the corresponding HECs or HEDs obtained by the default methodology. No animal-to-human UFs were applied in this comparison.

As shown in Table 2, the correct relationship for cross-species dosimetry depends on whether the toxicity is due to the parent chemical or a metabolite, and in the case of toxicity from a metabolite, whether the metabolite is highly reactive or sufficiently stable to enter the circulation. Moreover, the nature of the cross-species relationship for each of these possibilities is different for oral exposure than for inhalation. Therefore, pharmacokinetic modeling is required to improve the reliability of cross-species extrapolation that considers the nature of the toxic entity.

Default noncancer risk assessments apply a UF of 10 for uncertainty regarding animal-to-human extrapolation. This UF is applied to consider the possibility of both pharmacokinetic and pharmacodynamic differences between rodents and humans that could put the human at greater risk (i.e., result in toxicity at lower exposures) and is reduced to 3 when inhalation dosimetry is used to consider pharmacokinetic differences (*42*). A reduced factor of 3 has also sometimes been applied for data from species that are considered physiologically "closer" to humans, such as dogs or monkeys. This UF plays the same role, and is roughly the same magnitude as

Table 2. Alternative metrics for cross-species equivalence.

Route, basis	Metric	Human/animal dose equivalence ratio
Inhalation		
Default		
1986 U.S. EPA cancer guidance (*45*)	Inhaled dose × $(A/H)^{1/3}$	0.15–0.3
New U.S. EPA cancer guidance (*44*)	TWA Conc (PD:UF = 1–10)	1
U.S. EPA noncancer guidance (*42*)	TWA Conc (PD:UF = 3)	1
Allometric		
Parent chemical	TWA Conc	1
Reactive metabolite	TWA Conc/$(A/H)^{1/4}$	4–7
Stable metabolite	TWA Conc	1
PBPK[a]		
Parent chemical	Parent AUC	0.6–1.7
Reactive metabolite	Tmet/Vt	5–25
Stable metabolite	Metabolite AUC	0.1–1
Oral		
Default		
1986 U.S. EPA cancer guidance (*45*)	Dose × $(A/H)^{1/3}$	0.08–0.16
New U.S. EPA cancer guidance (*44*)	Dose × $(A/H)^{1/4}$	0.15–0.25
U.S. EPA noncancer guidance (*42*)	Dose (PK+PD:UF = 10)	0.3
Allometric		
Parent chemical	Dose × $(A/H)^{1/4}$	0.15–0.25
Reactive metabolite	Dose	1
Stable metabolite	Dose × $(A/H)^{1/4}$	0.15–0.25
PBPK[a]		
Parent chemical	Parent AUC	0.01–0.1
Reactive metabolite	Tmet/Vt	1–2
Stable metabolite	Metabolite AUC	0.02–0.07

Abbreviations: A/H, animal to human body weight ratio; Conc, concentration; PD, pharmacodynamic; PK, pharmacokinetic; Tmet/Vt, total metabolite formed in tissue divided by tissue volume.

[a] Based on physiologically based pharmacokinetic (PBPK) modeling of methylene chloride, trichloroethylene, and vinyl chloride.

the traditional use of body surface area scaling in cancer risk assessment (which resulted in a factor of about 7 for rats and 13 for mice) (Table 1). In both cases the concern that the human might receive a relatively greater exposure, and hence be at relatively greater risk, than smaller animals receiving the same nominal dose reflects years of experience with data on chemical toxicities that, for the most part, arise from oral exposure to chemicals that are directly toxic (i.e., as the parent compound, without the need for metabolic activation) (*3*).

As shown in Table 2, the human is indeed predicted to be at greater risk for oral exposures to chemicals that are directly toxic due to the effect of pharmacokinetic scaling. For oral exposures to a toxic chemical that must be cleared by metabolism or urinary excretion, the internal exposure (AUC) in the human is greater than in smaller animals at the same administered dose because the clearance of chemicals, both metabolic and urinary, tends to decrease relative to body weight as the animal becomes larger (*46*). In fact, the allometric scaling of clearance appears to follow body weight raised to the three-quarters power, producing slightly less of a difference across species than that predicted by body surface area scaling, which is body weight raised to the two-thirds power (*35*). Indeed, based on a multiagency analysis of the evidence for cross-species scaling factors, the U.S. EPA (*35*) changed from its default body surface area cross-species scaling for cancer to a new scaling approach based on body weight raised to the three-quarters power.

In both cancer and noncancer risk assessment, there is continuing controversy regarding the appropriate cross-species default for pharmacodynamics. The origin of the default scaling/UF actually applied in either case rests on observations of relationships across species, which are completely consistent with pharmacokinetics alone (*3*). Nevertheless, the use of pharmacokinetics in a cancer or noncancer risk assessment has never been considered to fully replace the default scaling/UF. It can be seen from Table 2 that, in the case of noncancer risk assessment, the default approach is not necessarily conservative in all cases, even with the application of the full animal-to-human UF of 10 (e.g., compare the human/animal equivalence ratio 0.1 for the default approach with ratios ranging from 0.01 to 0.1 predicted with pharmacokinetics for the parent compound AUC). That is, in some cases, the cross-species differences in pharmacokinetics alone may exceed the default factor applied for both pharmacokinetics and pharmacodynamics. A similar result would be obtained for cancer risk estimates. Particularly in the case of toxicity due to a stable metabolite, the default dosimetry and scaling/UF may sometimes underestimate the human risk (overestimate the HEC/HED).

Cross-route extrapolation. Another important use of pharmacokinetics in risk assessment is for extrapolation from one exposure route to another. In default noncancer and cancer risk assessment approaches, no provision is made for the use of toxicity data from a different route than the human exposure of concern. Thus, for example, in performing an inhalation risk assessment for a chemical, data from animal studies performed by the oral route could not be included in the quantitative dose–response calculations. Except in the case of exposure–route-specific portal-of-entry effects, the use of pharmacokinetic modeling makes it possible to combine data from different routes in a quantitative risk assessment. Specifically, the pharmacokinetic model can be used to predict the target tissue dose associated with an animal toxicity study conducted by one route, and then can be exercised to predict the equivalent human exposure by another route that would result in the same target tissue dose (*22*).

Dose extrapolation. A third use of pharmacokinetics in risk assessment is to incorporate dose-dependent pharmacokinetics and metabolism into the dose–response calculations for a chemical. For example, the observed dose–response relationship between the exposure concentration and resulting toxicity of vinyl chloride in animal studies is highly nonlinear due to the saturation of metabolism. When a pharmacokinetic model is used, however, and the tissue dose is expressed in terms of total metabolism, the dose response for toxicity becomes linear, improving the accuracy of dose–response modeling.

Time extrapolation. In some cases, pharmacokinetic modeling provides a more accurate method for extrapolating across exposure time frames than default methods such as the use of the TWA exposure concentration or average daily dose. For example, exposure to 100 ppm vinyl chloride for 8 hr will not be equivalent to exposure to 800 ppm for 1 hr due to saturation of metabolism at the higher concentration and rapid postexposure clearance of unmetabolized chemical by exhalation. In the latter exposure, total metabolism will be significantly lower than in the former, but the AUC for the parent chemical will be greater. However, for a highly lipophilic chemical with similar high-affinity, low-capacity metabolism, postexposure metabolism of chemical stored in fat tissues could result in nearly the same amount of metabolism from an exposure of a few hours as from a continuous exposure at the same concentration. In cases such as these, a pharmacokinetic model, which incorporates a realistic description of the dose response for metabolism, is necessary to determine the correspondence between exposures over different durations (*2,47*).

The nature of time extrapolation performed by a pharmacokinetic model will also be determined to a large extent by the dose metric selected. For example, the two dose metrics described for acute toxicity, C_{MAX} and AUC, respond very differently to changes in exposure duration. In the case of inhalation exposure involving a constant concentration, the concentrations in the blood and tissue quickly rise to a steady-state and then remain constant until the exposure is terminated, at which time they rapidly return to zero (except, perhaps, in the fat). Thus C_{MAX} will be relatively invariant for exposures ranging from tens of minutes to years. In contrast, for the same exposure scenario, the AUCs in the tissues will be roughly proportional to the length of exposure.

It should be recognized, however, that pharmacokinetic modeling is generally not very useful for extrapolating across widely different time frames (e.g., from acute to subchronic or from subchronic to chronic exposure durations). The principal determinants of the relationship between the effects of shorter-term and longer-term exposure are, to a large extent, pharmacodynamic factors such as fatigue, repair, and compensation. Therefore, the default approach in noncancer risk assessment, in which a UF is applied to account for uncertainty regarding the effect of significant differences in the duration of exposure, is still appropriate when pharmacokinetics is considered. For this reason, the dose metrics calculated with pharmacokinetic models for noncancer risk assessments of chemicals are usually calculated as average daily values, where the average is taken over the total duration of the exposure. For example, instead of calculating the total AUC over a 90-day exposure, the average daily AUC (which is equivalent to a daily average concentration) is calculated by dividing the total AUC by the total duration of the exposure in days (90 in this case). Persistent chemicals remain in the body long after exposure so the period of concern for noncancer risk assessment may not be limited to the exposure period. During this time there can be extensive changes in body composition that alter distribution and elimination. PBPK models are well suited for incorporating these aspects into the risk assessment.

Application of Pharmacokinetic Modeling in Risk Assessment

As should be apparent from the discussion thus far, the application of pharmacokinetic modeling in risk assessment is both chemical- and end point-specific. Therefore, it is not possible to completely describe the approach that should be taken under all possible circumstances. The application of pharmacokinetics in a particular case requires the use of scientific judgment and an understanding of the risk assessment process. Nevertheless, a number of steps can be described that will generally be required regardless of the details of the application.

Step 1: Selection of potential critical studies and organization of the mode of action literature. The first step in performing a risk assessment using pharmacokinetic modeling is essentially the same as in the default approach: evaluation of the available toxicologic and mechanistic data for the chemical and selection of potential critical studies. The principal difference is that, because the cross-species equivalence for different toxicologic end points may vary, as described above, it is not always possible to determine from a comparison of the animal exposure data which study will predict effects at the lowest human exposures. Another major difference is the importance of organizing information regarding the mode of action of the chemical for the critical end points. Both qualitative and quantitative data help determine the appropriate methods (e.g., choice of dose metric) in later steps.

Step 2: Selection of a pharmacokinetic model. Once the exposure scenarios and end points of concern have been selected, the requirements for a pharmacokinetic model can be determined. The key elements of this determination are the animal species and exposure conditions that the model must be able to simulate, and the target tissue dose metrics that the model must be able to calculate. Of course, it is also necessary to determine whether the model has been adequately validated to ensure its reliability for the intended purpose (*14*). In particular, the reliability of the model predictions for each of the dose metrics should be carefully evaluated (*48,49*).

Step 3: Calculation of dose metrics for toxicity studies and analysis of the potential critical studies. For each study and end point selected in step 1, the pharmacokinetic model is used to calculate the appropriate dose metrics for the end point of concern. In some cases, it may be possible to postulate more than one reasonable dose metric. In such cases, all of the candidate metrics should be calculated. The final decision regarding which metric to use should be made only after the calculations have been completed for each metric and should consider both the plausibility and conservatism of the various options, as will be discussed later. To calculate the dose metrics, the model parameters are set to those for the species represented in the study, whether experimental animals or humans. In the case of developmental studies, it is necessary to estimate parameters for a young animal or pregnant female rather than an average adult. To the extent possible, data from the study on animal strain, body weights, age, and activity should be used in selecting parameters for the model. The experimental parameters in the model are then set to reproduce the exposure scenario performed in the study, and the model is run for a sufficient period of time to characterize the animal exposure to the chemical and, if necessary, its metabolites.

There are often a number of options regarding the way in which the model should be run to characterize the exposure. These depend on the dose metric(s) selected as appropriate for further analyses based on the mode of action information. Frequently, a daily average is estimated, although in some cases the total over the duration of the experiment is used. As mentioned earlier, while the averaging period in the case of cancer is typically taken to be the lifetime, the averaging period in the case of noncancer risk assessment is considered to be the duration of the exposure or, perhaps, the critical window.

For short-term exposures, the model must be run for an appropriate period that reflects the dose metric being used and the timing of the measurement of toxicity in relation to the period of exposure. For short exposure, this is easily done by running the model for the total duration of the exposure (or exposures, for repeated exposure studies) to obtain dose metrics. If the animals were held for a postexposure period before toxicity was evaluated, the model must be run either until the end of the postexposure period or for a sufficient duration to ensure that the parent chemical has been completely cleared from the body or, for a dose metric based on a metabolite, a long enough time to ensure the complete clearance of the metabolite. The resulting dose metric obtained for the total duration of the exposure (including any postexposure period) can then be divided by the number of days over which the experiment was conducted to derive the average daily value.

The same approach (running the model for the total duration of the study) can be used to calculate dose metrics for longer-term exposures. This approach would typically be necessary for models that describe changes in the physiology or chemical handling during different lifestages (e.g., adolescence, aged). However, an alternative approach, which is often attractive for modeling chronic exposures with time-invariant model parameters, is to estimate the steady-state dose metric. There are two principal methods for calculating a steady-state estimate. In the first, the model is run until steady state is reached; the dose metric is then calculated by subtraction. For example, in the case of a chronic oral or inhalation exposure conducted 5 days/week, the model can be run consecutively for 1 week, 2 weeks, 3 weeks, and so on. To calculate the average daily AUC for a given week, the value at the end of the previous week is subtracted from the value at the end of the current week and the result is divided by 7. This process is repeated until the change in the dose metric from one week to the next is insignificant. For continuous exposures, the comparison can be made on a daily basis instead of weekly. The other method for estimating the steady-state dose metric is to estimate it from a single day exposure. The model is run for a single-day exposure plus an adequate postexposure period to capture clearance of the parent compound or relevant metabolite. This value of the single-day dose metric is then modified by the necessary factors to obtain an average daily value (e.g., by multiplying by five-sevenths in the case of the 5-day/week exposure). This method, which is faster but only approximate, is sufficiently accurate for estimating average daily AUC in many cases. It can be checked against the first method described to determine its accuracy in a particular case.

The dose metric calculations needed are determined by the method to be used for the noncancer or cancer analysis. If the NOAEL/UF method is being used in a noncancer risk assessment, a dose metric only needs to be calculated for the NOAEL or LOAEL exposure for a particular study and end point. If dose–response modeling is to be performed, such as in the benchmark dose approach (*50,51*), dose metrics must be calculated for all exposure groups. The dose metrics are then used in the dose–response model in place of the usual exposure concentrations or administered doses. It is important to remember that when this is done, the result of the dose–response modeling will also be in terms of a value of the dose metric rather than an exposure concentration or administered dose. Dose–response modeling is more properly conducted on the dose metrics because it is expected that the observed effects of a chemical will be more simply and directly related to a measure of target tissue exposure than to a measure of administered dose.

Step 4: Application of uncertainty factors. In the default noncancer risk assessment approach, animal exposure concentrations are converted to HECs before any necessary UFs are applied. In a pharmacokinetic risk assessment approach, on the other hand, it is more appropriate to divide the dose metrics corresponding to the point of departure (for cancer MOE) or the noncancer equivalents (e.g., NOAEL or benchmark dose) obtained from the toxicity studies by the necessary UFs rather than the HECs or HEDs. The rationale for applying the UFs to the dose metrics is the same as for using the dose metrics in dose–response modeling: the observed effects of a chemical are expected to be more simply and directly related to a measure of target tissue exposure than to a measure of administered dose. The dose metrics are specifically chosen to provide more useful measures of the biologically effective dose. Therefore, it is the dose metrics that should be adjusted to assure that the biologically effective dose is reduced to the extent desired. As a counterexample, consider the case in which toxicity has been observed for exposure to a chemical at a concentration well above the point where saturation of the metabolism of the chemical occurs and where the metabolism of the chemical is responsible for the toxicity. In this case, applying the UF to a dose metric based on total metabolism would assure that the extent of metabolism would be reduced by the same factor. However, if the concentration at which the effect was observed were sufficiently higher than the concentration at which metabolism is saturated, applying the UF to the exposure concentration might not actually reduce the extent of metabolism to any appreciable extent.

The selection of UFs in a pharmacokinetic risk assessment is essentially the same as for the default noncancer process described earlier, except that the UF for uncertainty in animal-to-human extrapolation should be reduced to reflect the use of pharmacokinetic modeling. By analogy to the U.S. EPA (*35*) approach for inhalation dosimetry, reduction of the default animal-to-human UF from 10 to 3 would seem to be reasonable for both inhalation and oral risk assessments. The remaining factor of 3 is then considered to represent uncertainty regarding pharmacodynamic differences across species and could be modified on the basis of other information for the chemical. The UFs will generally vary from one study to another, as well as from one end point to another, as dictated by the nature of the study (e.g., if only a LOAEL was identified) and the information associated with the end point (e.g., if there is evidence regarding the relative sensitivity of humans compared to the experimental species).

Step 5: Determination of human exposure. To convert a dose metric to an exposure concentration or administered dose, the pharmacokinetic model must be "run backward"; that is, the model must be run repeatedly, varying the exposure concentration or administered dose until the desired dose metric value is obtained. In the case of calculating the acceptable human exposure corresponding to a given toxicity study, the physiological, biochemical, and exposure parameters in the model are set to appropriate human values and the model is iterated until the dose metric obtained for the human exposure of concern, often continuous or daily lifetime exposure, is equal to the dose metric obtained for the toxicity study divided by the UFs. The dose metric should be calculated in an analogous way to the dose metric for the toxicity study; that is, if the dose metric in the toxicity study was expressed in terms of an average daily value, the dose metric used for calculating the associated human exposure should also represent an average daily value. For short-term exposures, where the model has been run for the total duration of the toxicity study and the total dose metric value has been calculated, the dose metric used for calculating the associated human exposure should usually be obtained for an exposure over the same time period. An exception to this rule is the case where it is anticipated that the short-term exposure of concern for the human may represent a short-term excursion against a background of chronic exposure. In this case, a more conservative approach may be preferred, in which a steady-state dose metric calculation is used for the human.

When a steady-state dose metric is used in both an experimental animal and in a human, the calculation of a steady-state dose metric in the human generally requires running the model for a much longer period of time than in the animal. In fact, the time required to reach steady-state in the human can be estimated by multiplying the time to steady state in the animal by the ratio of human to animal body weights raised to the one-quarter power. This concept of the allometric scaling of equivalent times is sometimes referred to as "physiological time" (*35,52*).

Step 6: Selection of preferred dose metric/study/end point. After calculations for potential dose–response values (i.e., RfD, RfC, cancer factors) have been performed for each of the candidate studies and end points, the most appropriate alternatives must be selected. There are two principal criteria for this selection: plausibility and conservatism. For each end point, priority should be given to the dose metric that, on the basis of the available evidence, appears to provide the most plausible basis for estimating the biologically effective dose. The plausibility of a given dose metric is determined primarily by two factors: its consistency with available information on the mode of action (mechanism of toxicity) and the consistency of its dose response with that of the end point of concern. The first factor was discussed above; the second refers both to evaluating the dose metric's ability to linearize the dose response for the associated end point within a study (internal consistency) and its ability to demonstrate a consistent quantitative relationship of dose metrics for positive versus negative exposures, regardless of differences in exposure scenario, route, and species (external consistency).

The dose metric used in the pharmacokinetic cancer risk assessment for vinyl chloride (*12*) demonstrated all of the attributes of an effective dose metric. First, the form of the metric (total daily metabolism divided by the volume of the liver) was consistent with the mode of action for the end point of concern (liver tumors), which involves DNA adduct formation by a highly reactive chloroethylene epoxide produced from the metabolism of vinyl chloride. Second, although the dose response for liver tumors versus exposure concentration of vinyl chloride is highly nonlinear with a plateau at several hundred parts per million, the dose response for liver tumors versus the metabolized-dose metric is essentially linear from 1 ppm to 6,000 ppm. Finally, and most impressively, when the potency of vinyl chloride liver carcinogenicity was expressed in terms of the metabolized-dose metric, essentially the same potency was calculated from both inhalation and oral studies in the mouse and rat, as well as from occupational inhalation exposures in the human. Although it is rare to find a case where there is such consistency across widely diverse studies, a dose metric that adequately represents the biologically effective dose should generally have lower values under exposure conditions with no effect and higher values for toxic exposures, regardless of differences in exposure scenario, route, or species.

The other criterion for the selection of the appropriate dose metric is conservatism. Where there is an inadequate basis for giving priority to one dose metric over another, the most conservative (the dose metric producing the highest risk or lowest acceptable exposure) would be used in order to be health protective. After selecting the most appropriate dose metric for each end point, the results across the various studies and end points should be evaluated using the same criteria—plausibility (i.e., internal and external consistency of dose-response) and conservatism—to arrive at the final recommendation. When a risk assessment is based on an end point in an animal experiment, it may sometimes be possible to evaluate data from human exposures as a test of the plausibility of the result, even though the data might not be adequate to serve as the basis for calculating an alternative value. Another useful exercise is to vary the physiological and biochemical parameters used in the model to determine the effect of human pharmacokinetic variability on the dose metric (*53*). In particular, the model can be used to evaluate whether selected groups may represent sensitive subpopulations (e.g., pregnant women, children, the obese, etc.) due to differences in exposure or pharmacokinetic factors.

Discussion

We have outlined a process for consistently using dosimetry information in a mode of action-based dose–response analysis. The first step is the evaluation of potential critical studies and the relevant mode of action information for the effect observed in the critical studies. Because the appropriate dose metric is selected based on the mode of action, different critical effects (i.e., effects that might form the basis for estimating acceptable exposures) may require different dose metrics. A PBPK model appropriately parameterized for the species in which the critical effects were observed is then selected (Step 2) and used to calculate the relevant dose metrics for the benchmark dose or NOAEL of the critical effects (Step 3). Uncertainty factors are then selected and applied to the dose metric description of the point of departure (Step 4). Next, a human parameterized model is used to estimate the exposure concentration that would produce the same value for the dose metric as that obtained from the animal study modified by the uncertainty factors (Step 5). Finally, the values obtained for the different studies are compared and used as appropriate for the purpose of regulation or analysis under consideration (Step 6). Generally, the study giving the lowest allowable exposure would be used for establishing acceptable exposure levels assuming lifetime daily exposure. If you were evaluating the potential for a specific target organ toxicity to occur due to a mixture of chemicals, you would select the value based on the critical study with that end point.

Many of the issues described in this paper with regard to the PBPK-based approach are equally applicable to the default risk assessment process. For example, the selection of a dose metric that is appropriate for the chemical and toxicity of concern, while more evident in the PBPK-based approach, is just as important in the default approach. A case in point is the question of whether concentration or AUC should be used for short-term exposure guidelines (*28*). Unfortunately, with the exception of the RfC dosimetry guidelines (*42*), the selection of dose metric is typically described more as a matter of policy than of scientific judgment. In this regard, the spirit of the recently proposed cancer guidelines (*44*) represents an important departure from previous guidelines, which identified defaults as policy positions and required substantial justification for departure from the default approach. In contrast, defaults under the new cancer guidelines are described as no-information alternatives, the use of which must be defended on the basis of the lack of chemical-specific information to support a more scientifically appropriate approach.

The analyses described in this paper have focused on the use of pharmacokinetics with empirical analyses of the dose response for the effect. This reflects the greater extent of our knowledge about pharmacokinetics and its modeling as opposed to our knowledge of toxicity and pharmacodynamic modeling. However, as pharmacodynamic models become available, they can be readily incorporated into the process described here. Pharmacodynamic models currently often only exist for the animal species in the toxicity study and human parameters values, or the appropriateness of the model structure for humans may be unknown. Under these circumstances, the model would be used much as the empirical models are used for benchmark dose analysis (Step 3). That is, the pharmacodynamic model would be used to better describe or predict the dose response in the animal study to obtain the point of departure for the subsequent analyses. At this time, this approach has largely been explored in the area of cancer analysis using clonal growth models (*54,55*).

The goal of research in pharmacodynamic modeling is to develop models that, like pharmacokinetic models, can be parameterized for both animals and humans. After meeting this goal, the chemical risk assessment process would be very similar to that described in this paper, except that both a pharmacokinetic and a pharmacodynamic model would be used to analyze the animal study (Step 3) and then human versions of both models would be used to determine the human exposure that would be protective of that effect occurring in humans (Step 5). As noted earlier for pharmacokinetic analyses, this use of pharmacodynamic modeling would represent a significant change in the issue of cross-species concordance. Biologically based analyses assume some degree of concordance in the mechanism of action, if not in the resulting toxicity. The current default position is that end points will be used with no assumption of concordance unless it is conclusively demonstrated to be an animal-specific mechanism. Although this may be a health protective position, as it stands, it is impossible to use mechanistic toxicology or modeling in risk assessment and impossible to improve our ability to predict human consequences based upon animal studies.

There is a continuing interest on the part of regulatory agencies concerning the use of PBPK modeling in chemical risk assessment. Although risk assessments using PBPK models have been proposed for a number of chemicals, for both cancer and noncancer end points, there are relatively few cases to date of the actual acceptance of PBPK-based risk assessments by agencies. The slow progress of the application of PBPK modeling in risk assessment may be due in part to the lack of a common expectation regarding the necessary elements of a PBPK-based approach. Our intent in this paper was to describe the essential elements of a preferred approach for applying PBPK modeling in a chemical risk assessment, whether for cancer or noncancer end points. We hope that, to the extent that PBPK-based risk assessments can adhere to a similar protocol, agencies will become familiar with the process and will begin to accept it.

Appendix 1. Allometric scaling for interspecies extrapolation.

$$TD = a \times BW^{b} \quad [1]$$

$$TD_A = a \times BW_A^{b} \quad [2]$$

$$TD_H = a \times BW_H^{b}, \quad [3]$$

where TD is toxic dose (milligrams), A is animal (e.g., rat or mouse), BW is body weight (kilograms), H is human; a is a constant, and b is a scaling exponent (e.g., 2/3 or 3/4).

By substituting $a = TD_A / BW_A^b$ (rearranged Equation 2) into Equation 3, the conversion of the animal dose expressed in milligrams to the human dose in the same units is obtained:

$$TD_H = \left(\frac{BW_H}{BW_A}\right)^{b} \times TD_A. \quad [4]$$

To obtain the relationship in the milligrams per kilogram units more typically reported in toxicology:

$$\frac{TD}{BW} = a \times \frac{BW^b}{BW} = a \times BW^{b-1}. \quad [5]$$

This equation is rearranged for animals:

$$a = \frac{TD_A}{\left(BW_A \times BW_A^{b-1}\right)}. \quad [6]$$

Substituting Equation 6 into Equation 5 (for humans) obtains the conversion of the animal dose expressed in milligrams per kilogram to the human dose in the same units:

$$\frac{TD_H}{BW_H} = \left(\frac{BW_H}{BW_A}\right)^{b-1} \times \frac{TD_A}{BW_A}. \quad [7]$$

Equivalently the equation may be written as

$$\frac{TD_H}{BW_H} = \left(\frac{BW_A}{BW_H}\right)^{1-b} \times \frac{TD_A}{BW_A}. \quad [8]$$

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